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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/508,978	11/19/2004	Patrick Hwu	230591	4494

45733 7590 12/04/2008

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EXAMINER	
DUFFY, BRADLEY	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
12/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/508,978	HWU ET AL.	
	Examiner	Art Unit	
	BRADLEY DUFFY	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8,11-22,25,28-30,58-63 and 68* is/are pending in the application.

4a) Of the above claim(s) *1-5,8,11-22,25,28-30,58,60-63 and 68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed on September 10, 2008, is acknowledged and has been entered. Claim 59 has been amended.

2. Claims 1-5, 8, 11-22, 25, 28-30, 58-63 and 68 are pending in the application. Claims 1-5, 8, 11-22, 25, 28-30, 58, 60-63 and 68 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in the reply filed January 18, 2007.

3. Claim 59 is under examination.

Priority

4. With respect to the issue of priority, Applicant has not submitted any evidence or arguments in the reply filed February 14, 2008, that claim 59 should receive benefit under USC §§ 119 and/or 120 of the earlier filing date of the 60/368,438, filed March 27, 2002.

Claim 59 does not properly benefit under 35 U.S.C. § 120 by the earlier filing dates of the priority document claimed, since the claim is rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and/or a sufficiently enabling disclosure.

Again, to receive benefit of the earlier filing date under 35 USC §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Accordingly, the effective filing date of claim 59 is deemed the filing date of PCT/US03/09707, namely March 23, 2003.

Grounds of Objection and Rejection Withdrawn

5. Unless specifically reiterated below, the grounds of objection and rejection set forth in the previous Office action mailed June 10, 2008, have been obviated or rendered moot by Applicant's amendment and/or arguments filed September 10, 2008.

For clarity, as noted in the previous Office action mailed October 18, 2007, the amendatory material to which Applicant has referred finds support in the specification, as originally filed, in paragraph [0021], beginning at page 5, by its reference to the sequences set forth in GenBank™ under accession numbers AAG29348, AF254069, AAG29349, and AF254070.

Response to the Statement under 37 C.F.R. 1.57 (f)

6. The statement under 37 C.F.R. 1.57 (f) filed September 10, 2008, is sufficient to satisfy the requirements set forth in 37 C.F.R. 1.57 (f) because the statement states that the material being inserted is the material incorporated by reference.

Grounds of Objection

Response to the Amendment

7. The amendment filed September 10, 2008, is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the addition of the paragraph that states:

> In another embodiment, the invention provides a method of inducing apoptosis of a natural killer (NK) cell comprising contacting the NK cell with a polynucleotide encoding SEQ ID NO: 6 or 8, in an amount effective to induce apoptosis of the NK cell in vivo.

Applicant has submitted that this amendment is supported by e.g., paragraphs 21, 42, 81-82, Figure 6 and Example 7.

Notably, Example 7 at page 32, presents the following relevant disclosure pertaining to Figure 6 and methods of inducing apoptosis of a natural killer cell:

> "As shown in Fig. 6a, annexin V staining of NKLI+/CD3" splenic NK cells increased from 16.9% to 41.6% 4 days after mIL-21 plasmid injection, indicating that mIL-21 had an apoptotic effect on NK cells in vivo. … These results demonstrate that IL-21 in vivo can induce NK cell apoptosis …".

Accordingly, while this disclosure sets forth a method of inducing apoptosis in murine NK cells *in vivo* by intravenous injection of a plasmid encoding a murine IL-21 polynucleotide into a mouse, after carefully reviewing the specification, including the claims as originally filed, the examiner could not find any other disclosure which would reasonably establish a nexus between the far broader subject matter set forth in the instant claims, which, for example, includes methods of inducing apoptosis in any NK cell from any species by contacting the NK cell in vivo with either an IL-21 polynucleotide encoding SEQ ID NO:8, which was derived from a mouse or an IL-21 polynucleotide encoding SEQ ID NO:6, which was derived from a human.

Accordingly, it is submitted that amending the specification to recite this far broader subject matter introduces new matter into the disclosure.

Otherwise this issue might be resolved if Applicant were to specifically point to other disclosures in the specification, including the claims, as originally filed, which are believed to support adding the above disclosure.

If this issue is not otherwise appropriately remedied, Applicant is required to cancel the new matter in the reply to this Office Action.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 101

8. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. The rejection of claim 59 is rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility, is maintained.

Once again, the considerations that are made in determining whether a claimed invention is supported by either a specific and substantial asserted utility or a well-established utility are outlined by the published Utility Examination Guidelines (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address; http://www.gpoaccess.gov.

Briefly, a "specific and substantial" asserted utility is an asserted utility that is specific to the particular nature and substance of the claimed subject matter, and which would be immediately available for application in a "real-world" context by virtue of the existing information disclosed in the specification and/or on the basis of knowledge imparted by the prior art, such that its use would not require or constitute carrying out further research to identify or reasonably confirm its usefulness in this context. A "well-established" utility is a credible, specific, and substantial utility, which is well known, immediately apparent, and implied by the specification, and based on the disclosure of the properties of a material or subject matter, either alone or taken with the knowledge of one skilled in the art.

Beginning at page 9 of the amendment filed September 10, 2008, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

As amended, Claim 59 is drawn to a method of inducing apoptosis of a natural killer (NK) cell comprising contacting the NK cell with a polynucleotide encoding SEQ ID NO: 6 or 8, in an amount effective to induce apoptosis of the NK cell *in vivo*.

In this case, Applicant appears to be arguing at page 9 that the claimed method has a specific and substantial utility to treat NK cell leukemias and NK lymphomas.

In response, this argument is not found persuasive, because, as set forth in the previous office action, the specification provides no asserted utility for the claimed

method other than the asserted utility of inducing apoptosis of a natural killer cell set forth in the method objective. Notably, a text search on the specification conducted on November 26, 2008, did not identify any relevant disclosure pertaining to causing apoptosis in NK cell leukemias and NK lymphomas and therefore, it is maintained that the specification does not assert a utility for the instant methods of treating NK cell leukemias and NK lymphomas.

Secondly, while Applicant has established that NK cell leukemias and NK lymphomas are known in the art, Applicant has provided no evidence that the claimed methods are supported by a "well-established" utility, which is well known, immediately apparent, and implied by the specification, and based on the disclosure of the properties of a material or subject matter, either alone or taken with the knowledge of one skilled in the art, because based on the evidence that NK cell leukemias and NK lymphomas are known in the art it is not apparent that treating NK cell leukemias and NK lymphomas using the claimed methods is an utility that is well known, immediately apparent, and implied by the specification. If it is Applicant's position that the claimed methods are supported by a "well-established" utility, Applicant is invited to supply further evidence that establishes that the claimed methods are supported by an utility, which is well known, immediately apparent, and implied by the specification, and based on the disclosure of the properties of a material or subject matter, either alone or taken with the knowledge of one skilled in the art.

Accordingly, after careful and complete consideration of Applicant's argument, for these reasons and the reasons of record set forth in the previous Office action, the specification does not provide a "specific and substantial" asserted utility for the claimed method and there does not appear to be a "well-established" utility for the claimed method, that would allow one of skill to use the claimed process in a "real world" context so as to immediately benefit the public. Therefore, the requirements set forth under 35 U.S.C. § 101 have not been met, and this rejection is being maintained.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. The rejection of claim 59 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is maintained. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth in above rejection of the claims under 35 U.S.C. § 101, one skilled in the art clearly would not know how to use the claimed invention.

Beginning at page 9 of the amendment filed September 10, 2008, Applicant has traversed the propriety of maintaining this ground of rejection by arguing that the method of claim 59 has a specific and substantial utility.

In response, Applicant's arguments have been carefully considered but not found persuasive because it is maintained that the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth in above rejection of the claims under 35 U.S.C. § 101.

12. The rejection of claim 59 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a NEW MATTER rejection.

Beginning at page 9 of the amendment filed September 10, 2008, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

As amended, claim 59, which was added after the filing date[1] of the instant application in the amendment filed July, 19, 2005, is drawn to a method of inducing apoptosis of a natural killer (NK) cell comprising contacting the NK cell with a polynucleotide encoding SEQ ID NO: 6 or 8, in an amount effective to induce apoptosis of the NK cell *in vivo*.

In this case, Applicant appears to be arguing that the amendment of the claims to recite that the process occurs in vivo has overcome the rejection, and further pointed to disclosures at paragraph 21, 42 and 81-82, in addition to the previously identified Example 7 and Figure 6, as supporting the subject matter of claim 59.

In this case, paragraphs 21, 42 and 81-82 set forth the following disclosure:

> [0021] IL-21 is a cytokine produced by CD4+ T cells that is structurally related to IL-2, IL-4, and IL-15 (Parrish-Novak et al., Nature 408, 57-63 (2000)) and is known to have potent effects on all classes of lymphocytes, including B, T and NK cells. It acts synergistically on T cells with a proliferative signal provided by anti-CD3 antibodies, and promotes expansion of mature B cells in response to stimulation through CD40. In addition, IL-21, in synergy with Fit3 ligand and IL-15, promotes expansion and differentiation of NK cells from bone marrow progenitors in vitro, and enhances lyric effector function against target cells in lysis assays. (Parrish-Novak et al. (2000), supra). The amino acid and nucleotide sequences of human IL-21 are known in the art and are publicly available at the National Center for Biotechnology Information (NCBD website as GenBank Accession Nos. AAG29348 and AF254069, respectively. Furthermore, the amino acid and nucleotide sequences of mouse IL-21 arc known in the art and are publicly available as GenBank Accession Nos. AAG29349 and AF254070, respectively.
>
> [0042] A further embodiment of the present invention relates to a method of treating or preventing a subject, preferably mammalian, more preferably human, having solid malignant tumors or lymphomas by administering to the subject an effective amount of an IL-21 plasmid suitable to reduce, ameliorate, and/or eliminate the tumor or lymphoma. The IL-21 plasmid DNA can be directly introduced into the solid tumor cells or nodules of the patient.
>
> [0081] Pharmaceutical compositions suitable for use in the present invention include compositions in which the active ingredients are contained in an effective amount to achieve the intended purpose. The determination of an effective dose or amount is well within the capability of those skilled in the art. For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., using neoplastic cells, or in animal models, usually mice, rabbits, dogs, or pigs. The animal model also can be used to determine the appropriate concentration range and route of administration. Such information then can be used and extrapolated to determine useful doses and routes for administration in humans.

[1] The filing date of the instant application is 11/19/04

> [0082] A therapeutically effective dose refers to that amount of active ingredient, for example, IL-21 polypeptide, or fragments thereof, activating antibodies to IL-21 receptor, agonists, or modulators of IL-21 polypeptide, which ameliorates, reduces, or eliminates the cancer, precancer, or immune-related disease, disorder, or condition. Therapeutic efficacy and toxicity can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., EDs0 (the dose therapeutically effective in 50% of the population) and LDs0 (the dose lethal to 50% of the population). The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as the ratio, LDs0/EDs0. Pharmaceutical compositions exhibiting large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used in determining a range of dosages for human use. Preferred dosage contained in a pharmaceutical composition is within a range of circulating concentrations that include the EDs0 with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

However, contrary to Applicant's assertion, and upon careful reviewing of the specification, it does not appear that the specification, including the claims, as originally filed, provide adequate support for claim 59, as currently presented. In this case, the additional disclosure pointed to by the Applicant does not reasonably establish a nexus between the far broader subject matter set forth in the instant claim, as explained in the previous office action, because this disclosure does not refer to methods of inducing apoptosis of a natural killer cell and therefore it is not apparent that far broader subject matter of inducing apoptosis in any NK cell from any species by contacting the NK cell in vivo with either an IL-21 polynucleotide encoding SEQ ID NO:8, which was derived from a mouse or an IL-21 polynucleotide encoding SEQ ID NO:6, which was derived from a human, was originally contemplated and envisioned by the inventors.

Furthermore, as explained in the previous Office action, while Example 7 sets forth a method of inducing apoptosis in murine NK cells *in vivo* by intravenous injection of a plasmid encoding a murine IL-21 polynucleotide into a mouse (see pages 31 and 32), the examiner could not find any other disclosure which would reasonably establish a nexus between the far broader subject matter set forth in the instant claims and this disclosure.

Given the apparent difference in the breadth of the claims and that of the pertinent disclosures, while Applicant's arguments have been carefully and fully considered, it is maintained that the instant claim has introduced new concepts,

violating the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

Otherwise this issue might be resolved if Applicant were to point to other disclosures in the specification, including the claims, as originally filed, which are believed to provide the necessary written support for the language of the instant claims.

Conclusion

13. No claim is allowed.

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The Examiner can normally be reached on Monday through Friday 7:00 AM to 4:30 PM with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

/bd/
Examiner, Art Unit 1643
November 26, 2008